SUBCLINICAL ADENOMA OF THE PITUITARY GLAND *

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INTRODUCTION

For many years the pituitary gland, or hypophysis cerebri, has been one of the favorite subjects for scientific investigation. In the early years of the present century interest in it, as indeed in most other organs, centered on its anatomical and pathological aspects. As physiological methods and knowledge improved, more and more attention was paid to its physiology, and in the past few years probably the chief interest has been in the latter field, particularly with reference to its effect on the other glands or organs of the endocrine system.

During this interval, however, and in spite of predominant interest in the physiology of the gland, several men, including Dandy and Rasmussen, investigating its anatomy, and Cushing and Bailey its pathology, have advanced our knowledge materially in these fields. The publication by Cushing [1,2] in 1932 of a series of cases describing a clinical syndrome often associated with basophilic adenoma reawakened general interest in some of the pathological manifestations of the pituitary gland. This renewed interest centered particularly around those long neglected and minute adenomas which occur in the anterior part of the pituitary gland and which I propose to call subclinical adenomas. Up to the present these adenomas have been considered chiefly as pathological curiosities.

Adenomas of microscopic size or larger are found to occur rather frequently in the glands of the endocrine system. Adenomas in the thyroid gland are so frequent as to be almost normal findings. Adenomas of microscopic size or larger are found in at least 25 per cent of all suprarenal glands examined at autopsy. The kidney, while not an endocrine organ, may be the site of numerous tiny adenomas in

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both the cortex and medulla and these adenomas may not produce any clinical symptoms. The prostate gland, again not an endocrine organ but one perhaps with some endocrine functions, shows a marked tendency to adenomatous formation with advancing age. For this reason it would be reasonable to suppose that symptomless adenomas in the pituitary gland should not be particularly uncommon.

It was not the purpose of this investigation to attempt to refute claims as to the clinical significance or insignificance of these adenomas. All of those in the present series were found in the pituitary glands of subjects who, at least so far as can be determined, had died of causes unrelated to disease in that gland. The study was undertaken chiefly to determine how frequently adenomas occur in supposedly normal pituitary glands, and incidentally to learn the ratio of frequency of adenomas composed of the three types of cells that are found normally in the anterior lobe, that is, chromophobic, eosinophilic and basophilic cells.

Such adenomas in the anterior lobe of the pituitary gland have been recognized for many years. Erdheim [3] in 1903 mentioned finding 2 adenomas of minute size in the hypophysis, both of which were apparently composed of basophilic cells. Löwenstein [4] in 1907 mentioned finding 2 more, but he neglected to mention their cell type. Erdheim and Stumme [5] in 1909, writing on the changes in the anterior lobe of the pituitary in pregnancy, reported finding 10 minute adenomas in 118 cases, or in 8.4 per cent. Roussy and Clunet [6] in their paper on tumors of the anterior lobe of the pituitary in 1911 also mentioned small adenomas found at autopsy that had apparently not caused clinical symptoms.

In spite of Erdheim and Stumme's [5] report of an incidence of approximately 10 per cent, these adenomas continued to be considered very rare until 1933, when Roussy and Oberling [7] stated that adenomatous foci occurred in 10 per cent of the pituitary glands examined at autopsy; however, they gave no statistics on the number of cases. In the same year Susman [8] found 23 adenomas in 22 of 260 pituitary glands from routine postmortem examinations, a percentage again of 8.4. Of these 23 adenomas 8 were composed of basophilic cells, 6 of eosinophilic cells and 5 of chromophobic cells; the remainder were not classified. These adenomas varied in size from 0.2 to 25 mm. In 1934 Close [9] reported that the incidence of

pituitary adenomas was approximately 10 per cent in a series of routine postmortem examinations, but that it ran as high as 44 per cent in those cases in which there was associated carcinoma in other glands. Many others, such as Stolkind,[10] Wall and Hoyle,[11] Pritchard,[12] Rutishauser,[13] Weber,[14] Russell, Evans and Crooke,[15] Moehlig,[16] Bishop and Close,[17] Teel,[18] Wieth-Pedersen,[19] Kraus,[20] Reichmann,[21] Anderson,[22] Bauer and Wassing,[23] Roch,[24] Craig and Cran,[25] and Ulrich,[26] have reported 1 or more cases of basophilic adenoma associated with the syndrome known as pituitary basophilism.

Source and Preparation of Material

The material for this study consisted of 1000 pituitary glands obtained over a period of years in the course of routine postmortem examinations in which permission to examine the brain had been granted. The pituitary gland was removed in these cases by clipping off the posterior clinoid processes with bone forceps and removing the gland *in toto*. It was then placed in 10 per cent formalin solution and stored.

In preparing the sections the glands were removed from the formalin and cut into sagittal sections paralleling the longest axis. Since the glands vary greatly in shape and size, this method resulted in sections from some glands being parallel to the anteroposterior diameter, whereas others were transverse. The sections were cut by hand in thicknesses varying from 1 to 1.5 mm. Since the majority of adenomas were found to be 1.5 mm. or larger in diameter, it was felt that by this method the likelihood of many being missed on section was fairly remote. It might be mentioned at this point that attempts to identify adenomas in the freshly cut sections were in most cases futile.

These sections were then placed in Zenker's fluid for 24 hours to facilitate later staining by the Mallory-Heidenhain method. They were then embedded in paraffin in the ordinary manner and two sections, 10 microns in thickness, were cut from each paraffin block and these were mounted and stained with hematoxylin and eosin in the usual way. By this method three to ten sections from each gland were stained. The hematoxylin and eosin sections were examined grossly and microscopically, and in those cases in which adenomas were found another section was cut from the corresponding block of tissue

and stained by the Mallory-Heidenhain method, as outlined by Kernohan,[27] to determine the types of cells composing the adenoma. With this stain the cytoplasm of the chromophobic cells either does not stain at all or is pale blue; the eosinophilic granules stain bright red and the basophilic granules stain dark blue. These sections were then used to classify the adenomas as to their cell types.

Characteristics of Adenomas

At this point it becomes necessary to consider what constitutes an adenoma. The basophilic cells in particular have a tendency to occur normally in clumps or islands, which on superficial examination look like small adenomas but are probably merely normal architectural variations. Probably there can be no absolute criterion by which one can differentiate true adenoma formation and unusual structural variations. The smaller adenomas in the anterior lobe of the pituitary have no demonstrable capsule, and even in the larger ones what at first glance appears to be a capsule is merely a condensation of the cells surrounding the adenoma. In the majority of cases, however, there is no difficulty in distinguishing between an adenoma and a structural abnormality. The majority of adenomas found were spherical or nearly so (Fig. 1) and the larger ones were well demarcated by the ring of compressed pituitary cells surrounding them.

Another distinguishing factor is that in an adenoma the percentage of one particular type of cell in a given area is a great deal higher than in the normal portions of the gland. Moreover, the cell pattern differs from the normal arrangement of acini bordering vascular sinuses. In some of the adenomas the pattern resembles the honeycomb arrangement of pavement epithelium (Fig. 2); in others it looks like a markedly convoluted papilloma (Fig. 3) or compound tubular gland (Fig. 4). In still others there is no apparent structure, but the cells appear to be scattered loosely around a few vascular sinuses, with little connective tissue framework. Some also reveal areas of degeneration, necrosis and vacuole formation.

Just as the structure of the adenomas varies greatly, so do the cells show marked variability in appearance in different adenomas. In some, as in those appearing to be composed of pavement epithelium (Fig. 2), the cells are large and clear with centrally placed

and somewhat pale staining nuclei. In others the cytoplasm is somewhat scanty, the outline of the cell irregular, and the nucleus eccentrically placed. While the cells differ greatly in appearance in different adenomas, even in those made up of the same type of cells, in general they are fairly constant in a given adenoma. It was also noted that there was marked variability in the staining characteristics of different adenomas of the same type. In the eosinophilic and basophilic adenomas the color ranged from pale pink to deep red in the former and from pale lavender to deep blue in the latter. The cell types were determined by the presence of typical granules. Variations in color were not due to faulty staining technic, for the normal parts of the gland which were used as controls stained normally.

It was not found that the adenomas had any definite site of predilection for the anterior lobe, although the majority tended to be more peripherally than centrally located. Some projected from the surface of the gland under the capsule (Fig. 5), whereas others were embedded deep in the substance of the gland. Many occurred along the border contiguous to the pars intermedia, and in this region they tended to lose their spherical shape and become flattened at the intermedial pole (Fig. 6).

Adenomas were found composed of each of the three types of cell normally found in the pituitary gland. Rasmussen [28-30] has found that, in a series of pituitary glands from adult males, the anterior lobe contains on the average of 52 per cent chromophobic cells, 37 per cent eosinophilic cells and 11 per cent basophilic cells. The proportion in the glands of adult females is only slightly different from that in males. One would therefore expect that if these three types of cell were all actively growing and reproducing themselves, as some histologists believe, then in a large series of cases adenomas composed of the different types of cells should occur in about the same ratio of frequency as the cells themselves normally occur. This, however, was not found to be the case, as will be shown later.

Experience with operative specimens of pituitary tumors has shown that they are frequently composed of mixed cells. This is also true of subclinical adenomas. Not more than two or three adenomas in the series were composed of purely one type of cell; the majority, on the other hand, had one type predominating sufficiently to classify the adenoma according to this predominant type of cell. In a few

cases, however, two or even three types of cells occurred in almost equal proportions in the same adenoma, so it was necessary to classify them merely as mixed types.

In some cases more than 1 adenoma was found in a single gland. In several of these cases 2 adenomas were found to be associated, in some cases being similar types; in other cases two different types of adenoma were present. In 2 cases, 3 distinct adenomas were found, and in 1 of these cases all three types of adenoma were represented. In another case several adenomas were found, of various sizes and representing various types of cells; semiserial sections indicated that there were 10 or more separate and distinct adenomas in this one pituitary gland.

Frequency of Occurrence

Of the 1000 pituitary glands examined, 225 were found to contain 1 or more adenomas. In 224 of these glands, excluding the one with the multiple adenomas, there were found to be 265 adenomas. These adenomas were classified as follows: chromophobic, 140 (52.8 per cent); eosinophilic, 20 (7.5 per cent); basophilic, 72 (27.2 per cent); and mixed types, 33 (12.4 per cent).

Age Incidence

In an endeavor to find the age group in which adenomas most frequently occurred, the ages of those subjects with adenomas were plotted against the age curve for the 1000 subjects in the whole series. These latter had ranged from stillborn infants to a man of 99 years. The youngest subject in whom adenomas were found was 2 years old, the oldest was 86 years old.

As can readily be seen from Chart 1, the greatest incidence of adenomas occurred in the sixth decade of life; however, since the greatest amount of autopsy material also occurs in this decade, the curve in Chart 2 was plotted from the ratio of adenomas to pituitary glands in each age group. This shows even more conclusively that the highest incidence of such adenomas occurs in the sixth decade of life (Chart 2). Because of the relatively small number of subjects who were more than 70 years of age, the end of the curve is indefinite and inconclusive.

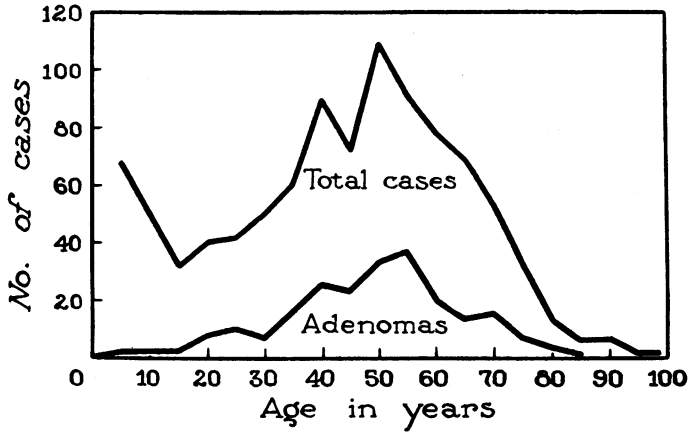

CHART 1. The ages in which adenomas occurred and the age groups in which the pituitary glands were obtained.

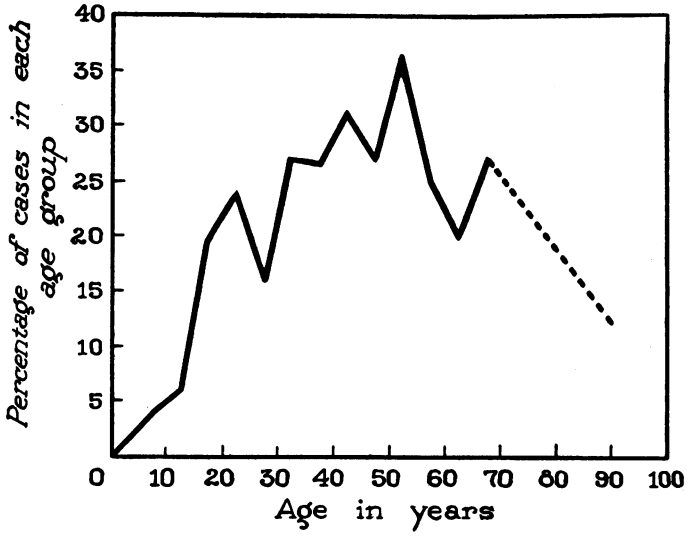

CHART 2. This graph was plotted by dividing the number of adenomas found in each age group by the total number of pituitary glands derived from subjects in that age group.

Sex Incidence

Of the 225 cases in which adenomas were found, 148, or 66 per cent, of the patients were males, 77, or 34 per cent, females. This would seem to indicate the predominance of adenomas among males. However, since the proportion of males to females in the 1000 cases was 63 to 37 per cent, it can be seen that the incidence in the two sexes is about equal.

Clinical Features

As has been mentioned before, the 1000 pituitary glands were obtained in a series of routine postmortem examinations in which permission to examine the cranial cavity had been granted. The clinical diagnoses and causes of death in these cases ranged through almost the entire list of medical and surgical conditions. As one would suspect from the age curve, diseases of middle life, such as cardiac failure, hypertension, nephritis and carcinomatosis, were more frequent than some other conditions, although the causes of death ranged all the way from stillbirth, through suicide, to senility. In the 225 cases in which adenomas were found the same variability in clinical findings and causes of death were apparent. The most notable thing about them was that there was nothing in the history or clinical findings in any case in which an adenoma was found to suggest the presence of any pituitary dysfunction. This was true in cases in which basophilic or eosinophilic adenomas were present as well as in those in which the adenomas were chromophobic. This is somewhat startling since in a few cases the adenomas were so large as almost to destroy the gland. Apparently, however, there was sufficient normal tissue remaining to sustain normal pituitary function.

Proportion of Different Types of Adenoma

As can be seen from the percentages of the different types of adenoma, the chromophobic adenomas occurred in about the same proportion as the chromophobic cells themselves occur in normal glands. With the eosinophilic and basophilic adenomas, however, there is considerable discrepancy. Although eosinophilic cells constitute 37 per cent of the normal hypophyseal cells, the eosinophilic adenomas represent only 7.5 per cent of the total number of adenomas. On the other hand, although the basophilic cells comprise only

11 per cent of the average normal cell content of the anterior lobe, basophilic adenomas made up 27 per cent of the total group of adenomas. It might be imagined that if the eosinophilic adenomas are more active than the other types, they might grow faster and give clinical symptoms early, since the majority of clinically recognized chromophilic adenomas occur before the age of 50 years. However, in the group of adenomas reported here the average age was greater than 50 years, and so this explanation is not warranted.

Of the 33 mixed types of adenomas, 21 were composed of mixed basophilic and eosinophilic cells; the remaining 12 consisted of chromophobic and basophilic cells with very few eosinophils.

Summary and Conclusions

It has been shown, therefore, that small adenomas of the anterior lobe of the pituitary gland, instead of being relatively rare pathological curiosities, occur with considerable frequency, since they occurred in 22.5 per cent of a series of 1000 unselected cases, or in nearly 1 out of every 4. Thus, the anterior hypophysis is shown to act much like other glands of the endocrine system in its tendency toward formation of adenomas.

It has been shown further that, like adenomas in other organs of the body, adenomas of the anterior lobe of the pituitary gland occur with increasing frequency in the higher age groups, and that they also apparently occur in the same proportion in both sexes.

It has also been shown that the majority of adenomas of the anterior lobe of the pituitary, irrespective of type, are entirely benign and give no recognizable clinical symptoms, and that they can be demonstrated only by rather detailed examination of the gland at autopsy. This would justify the term "subclinical adenoma" as applied to them. It is entirely possible, however, that under the influence of some unknown stimulus some of these adenomas may secrete a hormone or similar substance capable of producing clinical symptoms.

The chromophobic adenomas have been seen to occur in about the same relative proportion in the series as do the chromophobic cells themselves in the average normal gland. However, the eosinophilic and basophilic adenomas do not occur in the same relative proportions as their respective cells do in the average normal gland, and an adequate explanation for this has not been found.

Future work is yet to be done on the group of basophilic adenomas in this series in an attempt to tabulate and correlate their clinical features.

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DESCRIPTION OF PLATE

PLATE 24

FIG. 1. Chromophobe adenoma. The tendency to spherical shape, as well as the condensation of cells around the periphery, forming a pseudocapsule, is evident. Hematoxylin and eosin stain. × 23.

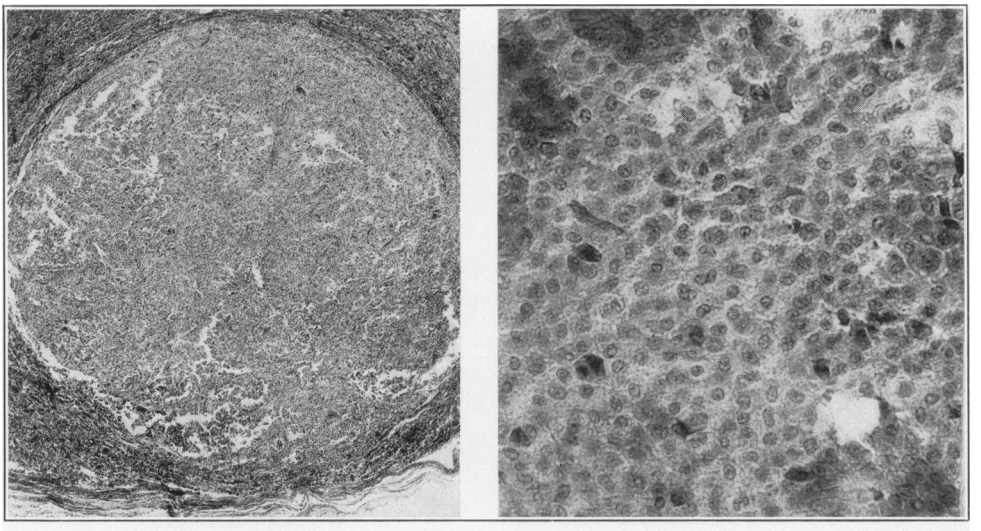
FIG. 2. Chromophobe adenoma. The adenoma cells arranged like pavement epithelium. Mallory-Heidenhain stain. × 300.

FIG. 3. Basophilic adenoma. The arrangement of cells resembles that of a convoluted papilloma. Mallory-Heidenhain stain. × 48.

FIG. 4. Chromophobe adenoma. The resemblance to a compound tubular gland is evident. Mallory-Heidenhain stain. × 85.

FIG. 5. Chromophobe adenoma. The adenoma budges the capsule of the pituitary gland. Hematoxylin and eosin stain. × 18.

FIG. 6. Eosinophilic adenoma. The adenoma is triangular and one side is against the pars intermedia of the pituitary gland. Hematoxylin and eosin stain. × 60.



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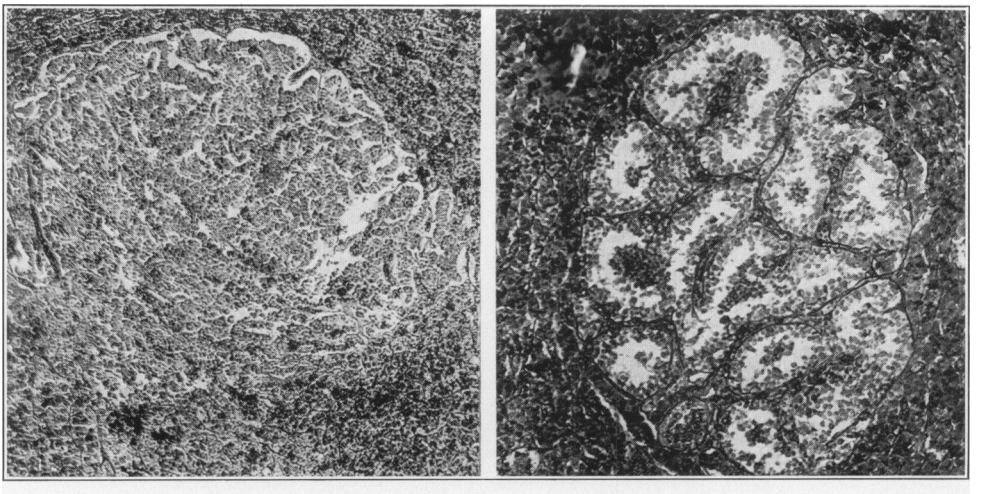

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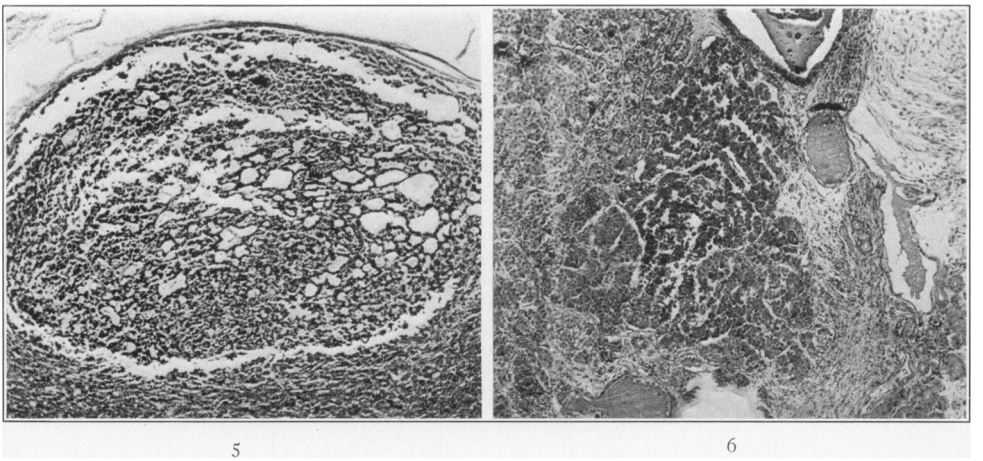

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